EXHIBIT 602.12

Medical treatment of heart disease

238
PHARMACOLOGIC TREATMENT OF CARDIOVASCULAR DISORDERS

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The clinical pharmacology of positive inotropic agents (digitalis glycosides and sympathomimetic agents), antiarrhythmic drugs, and coronary vasodilator agents is presented in this chapter. Diuretics and vasodilators are discussed in Chap. 236, antihypertensive agents in Chap. 251, and adrenergic blocking agents in Chap. 72.

The *direct* cardiac action of drugs may be divided into four major areas: (1) an effect on contractility (inotropic effect), reflecting alterations in the myocardial force-velocity relation at any given initial muscle length (Chap. 235); (2) an effect on heart rate, expressed as an alteration in the rhythmicity, i.e., the frequency of discharge of normal pacemaker tissue, generally that in the sinoatrial node; (3) an effect on conductivity, i.e., on the velocity with which the depolarization wave travels through the myocardium and the atrioventricular conduction system; and (4) an effect on irritability, i.e., the tendency to develop ectopic pacemaker activity, which is dependent on the rate of diastolic depolarization and the threshold potential (Chap. 237). In addition to these direct effects, drugs may also affect any of or all these four properties *indirectly* by altering (1) autonomic influences acting on the heart directly or reflexly, or (2) the relationship between myocardial oxygen supply (determined largely by coronary blood flow) and oxygen needs (Chap. 244).

DIGITALIS GLYCOSIDES

The basic molecular structure of the digitalis glycosides is a steroid nucleus to which an unsaturated lactone ring is attached at C-17 (Fig. 238-1*A*). These two elements together are called *aglycone* or *genin,* and it is this portion of the molecule which is responsible for the cardiotonic activity. The addition of a sugar to this basic structure enhances both the potency and duration of action of the glycoside, probably as a result of increasing solubility. The sugar residue may prevent alterations in the steric structure of the molecule, which would result in a loss of cardiotonic activity.

PHARMACOKINETICS Although, in the absence of severe malabsorption, digitalis is adequately absorbed from the intestinal tract even in the presence of vascular congestion secondary to heart failure, some glycosides, including ouabain, are poorly absorbed and, therefore, are effective only when administered parenterally; the intravenous route is preferable to the intramuscular, since absorption is erratic with the latter. When they are administered orally, absorption is close to complete within 2 h. The fraction of orally administered glycoside which

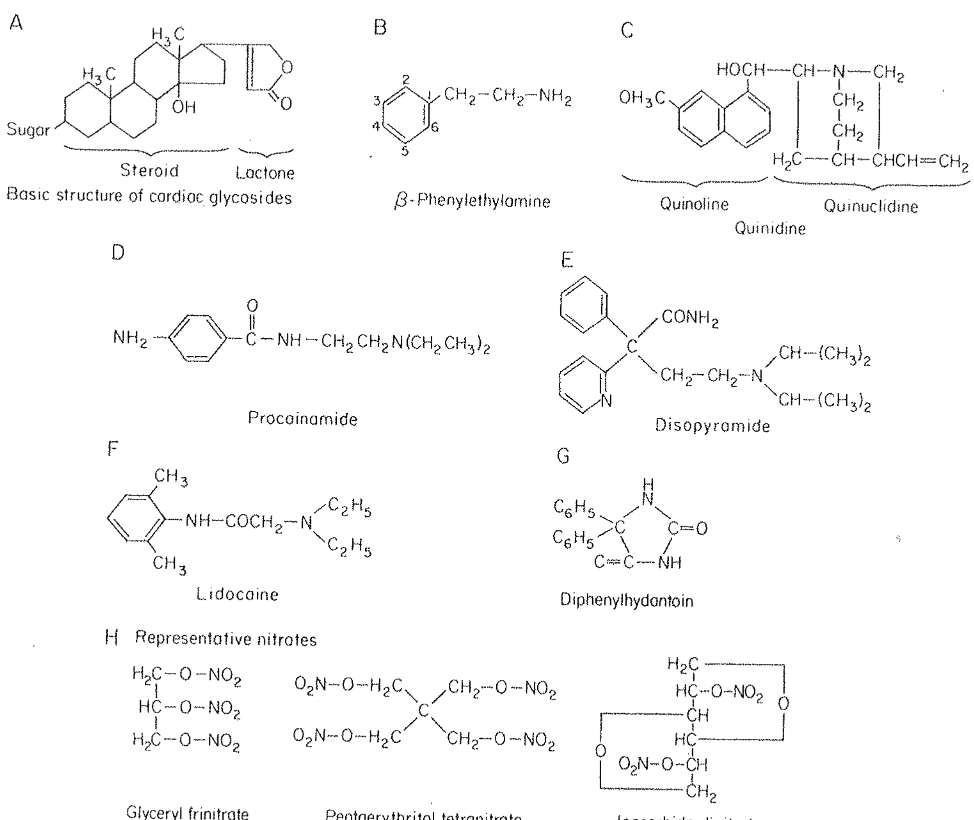

FIGURE 238-1 *Chemical structure of various cardioactive drugs.*

is absorbed varies. Approximately 40 percent of digitalis powder is absorbed, almost 100 percent of digitoxin, and 65 to 75 percent of digoxin. Considerable variability of bioavailability has been found in different commercial preparations of digoxin. Cholesterol-lowering resins, antidiarrheal agents containing pectin and kaolin, nonabsorbable antacids, and neomycin can reduce the absorption of digoxin and digitoxin. Varying degrees of protein-binding of glycosides occur in the bloodstream (for example, 97 percent for digitoxin and 25 percent for digoxin), and though these differences may account in part for the varying durations of the effect of different glycosides, they are not related to the speed of action of these drugs. The plasma contains only approximately 1 percent of the body stores of digoxin; digoxin is not effectively removed from the body by dialysis, exchange transfusions, or during cardiopulmonary bypass, presumably because of tissue binding. The major fraction of the glycosides is directly bound by various tissues including the heart, in which the concentration is approximately 30 times that in the plasma for digoxin and 7 times for digitoxin, which is less polar and more lipid-soluble than digoxin.

Digoxin, which has a half-life of 1.6 days, is filtered in the glomeruli, and 85 percent is excreted in the urine, most in unchanged form; only 10 to 15 percent of digoxin is eliminated in the stool through biliary excretion in the presence of normal renal function. The ratio of digoxin clearance to endogenous creatinine clearance is 0.8, and the percentage of the body's total stores of digoxin lost per day can be calculated as $(14 \pm 0.2) \times$ creatinine clearance in milliliters per minute. In patients with normal renal function a plateau concentration in the blood and tissue is reached after 5 days of daily maintenance treatment without a loading dose (Fig. 70-2). Therefore, significant reductions of the glomerular filtration rate reduce the elimination of digoxin (but not of digitoxin) and, therefore, may prolong digoxin's effect, allowing it to accumulate to toxic levels. The administration of most diuretics does not alter the excretion of digoxin significantly, but spironolactone can inhibit tubular secretion of digoxin, resulting in significant accumulation of the drug. Serum levels and pharmacokinetics are essentially unchanged by massive weight loss. *Digitoxin,* with a half-life of approximately 5 days, is metabolized chiefly in the liver; only 15 percent is excreted in the urine unchanged and an equal fraction in the stool. Drugs such as phenobarbital and phenylbutazone that increase activity of hepatic microsomal enzymes accelerate the metabolism of digitoxin. To reach a steady state, digitoxin requires maintenance doses for 3 to 4 weeks. *Ouabain* is very rapid acting, exhibiting an onset of action 5 to 10 min and a peak effect 60 min following intravenous injection. It is poorly absorbed from the gastrointestinal tract and, therefore, is not suitable for oral use; it is excreted by the kidneys, has a half-life of 21 h, and is useful in emergencies.

MECHANISM OF ACTION The cardiac actions of all digitalis glycosides are alike. The clinical effects result from augmenting contractility and irritability and from slowing heart rate and atrioventricular conduction. In addition, the cardiac glycosides potentiate vagal influences on the heart.

The most important effect of digitalis on cardiac muscle is to shift its force-velocity relation upward (Chap. 235). This positive inotropic effect is exhibited in normal, nonfailing hypertrophied as well as in failing hearts. In the absence of heart failure, however, when cardiac output is not limited by cardiac contractility, the drug does not elevate the output. The finding that digitalis increases the contractility of the nonfailing heart has led to its use (1) in patients with heart disease but without heart failure prior to operation or other stressful situations such as serious infections, and (2) in the presence of a chronically increased load, such as hypertension without heart failure. However, definitive evidence of its efficacy in these circumstances has not been provided.

Excitation-contraction coupling is the membrane and intracellular process most likely involved in producing the positive inotropic effect of digitalis glycosides. These drugs inhibit transmembrane sodium and potassium movement by inhibition of the magnesium and ATP-dependent sodium- and potassium-activated transport enzyme complex. The latter, localized to the sarcolemma, and termed Na^+- and K^+-stimulated ATPase, appears to be the receptor for cardioactive glycosides. There is a correlation between inhibition of the enzyme and the inotropic potency of the glycoside. The resulting altered transmembrane distribution of sodium, i.e., the elevation of the intracellular concentration of this ion, according to one theory, then competes with calcium for efflux at internal membranes, so that less calcium is transported out of the cell and more is available to activate contractile sites. According to another concept, the increased intracellular sodium concentration enhances transmembrane exchange of sodium and calcium. Regardless of the precise mechanism involved, there is an increased myocardial uptake of calcium, which augments calcium released to the myofilaments during excitation and, therefore, invokes a positive inotropic response.

The action of glycosides on the inhibition of the sarcolemmal Na^+- and K^+-stimulated ATPase also produces alteration in the electrical properties of both the contractile cells and the specialized automatic cells. While low concentrations of glycosides produce little effect on the action potential, high concentrations result in a reduction in the resting potential (phase 4) with an augmented rate of diastolic depolarization (Chap. 237). The reduction in the resting potential brings the cell closer to the threshold for depolarization. These two effects lead to increased *rhythmicity* and ectopic impulse activity. With the lowering of the resting potential, the rate of rise of the action potential is reduced, resulting in a slowing of conduction velocity, which is conducive to the development of reentry. Thus, the known electrophysiologic effects of digitalis glycosides are capable of explaining both reentry and ectopic foci and the resultant arrhythmias associated with digitalis intoxication.

The glycosides also prolong the *functional refractory period* of the atrioventricular node, through a direct action, as well as an enhanced vagal effect. Digitalis also shortens the refractory period of the atrial and ventricular muscle. Small action potentials are propagated in a decremental fashion in the atrioventricular junction. Most do not reach the ventricles but leave some of the atrioventricular junctional cells in a refractory state. Together with the action of digitalis to augment vagal activity, this helps to explain the slowing of ventricular rate produced by digitalis glycosides in supraventricular tachycardias. In atrial fibrillation, the slowing of ventricular rate is explained by several factors, in addition to prolongation of the functional refractory period of the atrioventricular node, including increased fibrillation rate (shortened atrial refractory period) and increased concealed conduction with fewer impulses penetrating the atrioventricular junction owing to both direct and vagal effects of glycosides on junctional tissue.

Digitalis exerts a negative chronotropic action, which in part is a vagal effect and in part is due to a direct action on the sinus pacemaker. In heart failure, slowing of the sinus rate following the administration of digitalis results also from withdrawal of sympathetic activity secondary to general improvement in circulatory status due to the positive inotropic effect of the glycoside. In the nonfailing heart the slowing effect is neg-

ligible, and digitalis should not be used for the treatment of sinus tachycardia unless heart failure is present. The apparent suppression of pacemaker activity which may take place following high doses of digitalis is probably due not to arrest of the pacemaker but rather to a sinoatrial block related to a depression of conduction.

In addition, the digitalis glycosides also exert an action on the peripheral vasculature, causing venous and arterial constriction in normal individuals and reflex dilatation resulting from withdrawal of sympathetic constrictor activity in patients with congestive heart failure.

INDICATIONS The most important indication for the administration of digitalis is congestive heart failure (Chap. 236). By stimulating the contractile function of the heart, digitalis improves ventricular emptying; i.e., it augments the ejection fraction, increases cardiac output, promotes diuresis, and reduces the elevated diastolic pressure and volume and end-systolic volume of the failing ventricle with consequent reduction of symptoms resulting from pulmonary vascular congestion and elevated systemic venous pressure. It is most beneficial in patients in whom ventricular contractility is impaired secondary to chronic ischemic heart disease, or when hypertensive, valvular, or congenital heart disease imparts an excessive volume or pressure load. Digitalis is also indicated in both the prevention and the abolition of recurrent episodes of paroxysmal supraventricular tachycardia. It is helpful in slowing the rapid ventricular rate of patients with atrial flutter and fibrillation (Chap. 237). It is of relatively little value in most forms of cardiomyopathy, myocarditis, beriberi with heart failure, mitral stenosis, thyrotoxicosis and sinus rhythm, cor pulmonale when the lung disease is not being treated concurrently (Chap. 246), and chronic constrictive pericarditis (Chap. 249). Nonetheless, it is not contraindicated in these disorders and is frequently used since it may exert a beneficial effect, albeit not a *striking one.*

Digitalis is of little hemodynamic or clinical benefit in cardiogenic shock secondary to acute myocardial infarction, but is usually moderately effective in pulmonary edema and milder forms of heart failure secondary to myocardial infarction. Digitalis has variable effects on angina pectoris, sometimes reducing this symptom in the presence of cardiomegaly and heart failure but tending to increase it in their absence. In patients with second-degree atrioventricular block, digitalis may be harmful by inducing complete (third-degree) block, and in those with idiopathic hypertrophic subaortic stenosis (Chap. 247) by increasing obstruction to left ventricular outflow.

DIGITALIS INTOXICATION Although digitalis is one of the cornerstones of the treatment for heart failure, it is a two-edged sword, because intoxication due to digitalis excess is a common, serious, and potentially fatal complication of its use. The therapeutic-to-toxic ratios are identical for all cardiac glycosides. In most patients with heart failure the lethal dose of most glycosides is probably 5 to 10 times the minimal effective dose and only about twice the dose which leads to minor toxic manifestations. In addition, old age, acute myocardial infarction or ischemia, hypoxemia, magnesium depletion, renal insufficiency, hypercalcemia, carotid sinus massage, electrical cardioversion (Chap. 239), and hypothyroidism all may reduce the tolerance of the patient to the digitalis glycosides or provoke latent digitalis intoxication. The most common precipitating cause of digitalis intoxication, however, is depletion of potassium stores, which often occurs as a result of diuretic therapy and secondary hyperaldosteronism. Since it is not necessary for a patient to receive a maximally tolerated dose of digitalis to derive a beneficial effect, even small doses provide some therapeutic action; this point should be considered if these drugs are to be used in patients prone to toxicity.

Anorexia, nausea, and vomiting, which are among the earliest signs of digitalis intoxication, are caused by direct stimulation of centers in the medulla and are not of gastrointestinal origin. The most frequent disturbance of cardiac rhythm caused by digitalis is premature ventricular beats, which may take the form of bigeminy because of increased myocardial irritability or facilitation of reentry. Atrioventricular block of varying degrees of severity may occur. Nonparoxysmal atrial tachycardia with variable atrioventricular block is quite characteristic of digitalis intoxication. Finally, sinus arrhythmia, sinoatrial block, sinus arrest, and atrioventricular junctional and multifocal ventricular tachycardia may also occur. These arrhythmias are due to action of the glycoside both on cardiac tissues and on the central nervous system. Chronic digitalis intoxication may be insidious in onset and characterized by exacerbations of heart failure, weight loss, cachexia, neuralgias, gynecomastia, yellow vision, and delirium. Digitalis-toxic cardiac arrhythmias precede extracardiac (gastrointestinal or central nervous system) toxicity in about one-half of cases.

Digitalis intoxication has been reported to occur in as many as 20 percent of hospitalized patients receiving a cardiac glycoside, which emphasizes the importance of the ability to diagnose this condition. The administration of quinidine to patients receiving digoxin raises the serum concentration of the latter and increases the incidence of digitalis intoxication. Therefore, serum digoxin concentrations and electrocardiograms should be followed carefully when quinidine is given to digitalized patients. The radioimmunoassays for digoxin and digitoxin make possible the correlation of serum glycoside levels with the presence of toxicity. In patients receiving standard maintenance doses of digoxin and digitoxin and in whom no sign of intoxication is present, serum concentrations approximate 1 to 1.5 and 20 to 25 ng/ml, respectively. When signs of intoxication are present, serum levels of more than 2 and 30 ng/ml, respectively, of these glycosides are often found. Since many factors other than the serum concentration determine digitalis intoxication, and since there is overlap in serum glycoside concentrations in patients with and without toxicity, it is clear that these levels cannot be used as a sole guide to digitalis dosage. However, when taken together with findings on the clinical examination and electrocardiogram, they add useful information to the clinical evaluations of digitalis intoxication. In addition they will indicate whether a patient for whom the history of digitalis intake is in doubt has, in fact, been receiving the drug.

Treatment of digitalis intoxication When tachyarrhythmias result from digitalis intoxication, withdrawal of the drug and treatment with potassium, phenytoin, propranolol, or lidocaine are indicated. Potassium should be administered cautiously and by the oral route whenever possible if hypokalemia is present, but small doses may also be helpful when serum potassium levels are normal; *potassium must not be employed in the presence of atrioventricular block or hyperkalemia,* when phenytoin is more appropriate. Propranolol should not be used to treat digitalis toxicity in the presence of severe heart failure or atrioventricular block; lidocaine is effective in the treatment of digitalis-induced ventricular tachyarrhythmias in the absence of preceding atrioventricular block. A cardiac pacemaker may be required in digitalis-induced atrioventricular block. Electrical conversion may not only be ineffective in treating these arrhythmias but may induce more serious arrhythmias (Chap. 239). However, it may be lifesaving in digitalis-induced ventricular fibrillation. Quinidine and procainamide are not useful in the treatment of digitalis intoxication. Fab fragments of pu-

which is further metabolized to acetylhydrazine, a potent hepatotoxin. Acetylhydrazine exerts its toxic effect through an active metabolite that binds covalently to macromolecules in the hepatic cells that produce it. Conversely, the lupus erythematosus-like syndrome produced by hydralazine (Chap. 251) occurs only in individuals who are slow acetylators.

Because these important toxic drug effects are largely predictable from the acetylation phenotype, it may in certain instances be of value to determine the rate of acetylation in patients who are to receive isoniazid, or those who would benefit from doses of hydralazine above the 200 mg per day dose that can be safely employed in the population at large. Acetylation phenotype can be determined by measuring the ratio of acetylated to nonacetylated dapsone or sulfamethazine in plasma or urine following administration of a test dose of these acetylation substrates. The ratio of monoacetyldapsone to dapsone in plasma at 6 h after dapsone administration is less than 0.35 for slow acetylators and greater than 0.35 for rapid acetylators. At 6 h following the administration of sulfamethazine, less than 25 percent of the drug in the plasma is in the acetylated form in slow acetylators (rapid acetylators, more than 25 percent); in the urine collected in the 5- to 6-h interval after administration, less than 70 percent of the drug is in the acetylated form in slow acetylators (rapid acetylators, more than 70 percent).

METABOLISM BY MIXED-FUNCTION OXIDASES In healthy individuals taking no other medications, the major determinant of the rate of metabolism of drugs by the hepatic mixed-function oxidases is genetic. In contrast to the bimodal distribution of individuals with respect to acetylation rates, there is a unimodal distribution for most drugs metabolized by enzymes of the hepatic endoplasmic reticulum, indicating control by multiple genes. The genetically controlled variation in hepatic clearance is marked for some of these drugs. Steady-state plasma levels of nortriptyline, propranolol, and chlorpromazine vary by more than tenfold among individuals. This has obvious consequences in attempting to predict effect from a given dose in those individuals who differ markedly from the average.

CONCENTRATION OF DRUGS IN PLASMA AS A GUIDE TO THERAPY

Optimal individualization of therapy is assisted by measuring the concentration of certain drugs in plasma. Genetic variation in elimination rates, interactions with other drugs, disease-induced alterations in elimination and distribution, and other factors combine to yield a wide range of plasma levels in patients given the same dose. Furthermore, the problem of noncompliance with prescribed regimens during continuing therapy is an endemic and elusive cause of therapeutic failure. There are clinical indicators that assist the titration of some drugs into the desired range, and no chemical determination is a substitute for careful observations of the patient's response to treatment. However, the therapeutic and adverse effects are not precisely quantifiable for all drugs, and in complex clinical situations estimates of the action of a drug may be misleading. For example, previously existing neurological disease may obscure the neurological consequences of intoxication with phenytoin. Because clearance, half-life, accumulation, and steady-state plasma levels are difficult to predict, the measurement of plasma levels is often useful as a guide to the optimal dose. This is particularly so when there is a narrow range between the plasma levels yielding therapeutic and adverse effects. The concept of the average dose will not benefit the patient whose levels are inadequate for therapeutic effect or in the toxic range. Adjustment of dosage based on creatinine clearance in renal insufficiency will minimize gross over- and undertreatment, but still it is a calculation based on an average and will not yield ideal treatment for all patients.

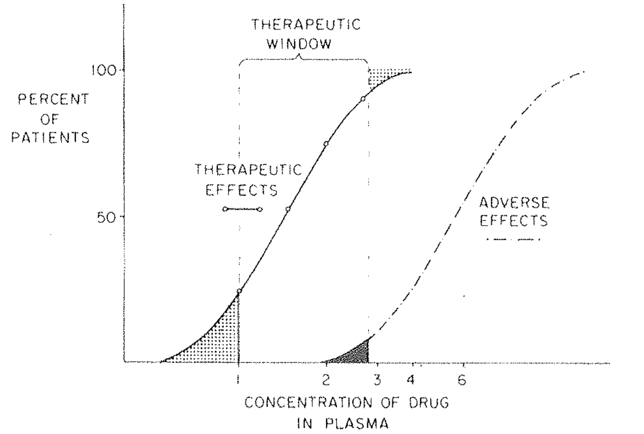

FIGURE 70-5

The cumulative percentage of patients responding to increasing levels of drug in plasma with both therapeutic and adverse effects. The therapeutic "window" defines the range of concentrations of drug that will achieve therapeutic effects in most patients with adverse effects in only a small percentage.

Data on concentrations of drugs in plasma are utilized most effectively in the framework of the known kinetics of the drug, including consideration of whether the levels are likely to reflect the steady state, whether they represent the equilibrium phase (cf., the distribution phase discussed above), and the extent to which disease-induced changes in the drug binding can influence the concentration of total (bound plus unbound) drug. In addition, the variability among individual responses to given plasma levels must be recognized. This is illustrated by a hypothetical population dose-response curve (Fig. 70-5) and its relationship to the therapeutic range or therapeutic "window" of desired plasma levels. The defined therapeutic window should include the levels at which the majority of patients will achieve the intended pharmacological effect. However, there are a few people who are quite sensitive to the therapeutic effects of most drugs, responding to lower levels, whereas others are sufficiently refractory as to require levels that impose an increased likelihood of adverse effects as a potential price for therapeutic benefit. For example, a few pa-

TABLE 70-4

Concentrations of drugs in plasma: relation to efficacy and adverse effects

Drug	*Efficacy**	*Adverse effects†*
Carbenicillin	100 μg/ml‡	300 μg/ml
Digitoxin	12 ng/ml	25–30 ng/ml
Digoxin	0.8 ng/ml	2.0 ng/ml
Gentamicin	4 μg/ml§	12 μg/ml
Lithium	0.5 meq/liter	1.3 meq/liter
Penicillin G	1-25 μg/ml¶	
Phenytoin (diphenylhydantoin)	10 μg/ml	20 μg/ml
Procainamide	4 μg/ml	8 μg/ml
Quinidine	3 μg/ml	7 μg/ml
Theophylline	8 μg/ml	20 μg/ml

* *The therapeutic effect is infrequent or slight at levels below these.*
† *The frequency of adverse effects increases sharply when these levels are exceeded.*
‡ *Minimal inhibitory concentration (MIC) for most strains of Pseudomonas aeruginosa. MIC for other, more sensitive, organisms is less.*
§ *Dependent on the MIC. Higher levels (up to 8 μg/ml) may be desired when host defenses are impaired.*
¶ *There is a wide range of MIC of penicillin for various organisms, and the MIC of all those for which penicillin is used is $<$ 20. "Massive" penicillin therapy with 20 million units daily achieves levels of 20 to 25 μg/ml in patients with clearance of creatinine of 100 ml/min.*

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